201-15210A

Test Plan for Quats

Dimethylaminoethylacrylate methylchloride [CAS No. 44992-01-0]

Dimethylaminoethylacrylate dimethylsulfate [CAS No. 13106-44-0]

Dimethylaminoethylmethacrylate methylchloride [CAS No. 5039-78-1]

Dimethylaminoethylmethacrylate dimethylsulfate [CAS No. 6891-44-7]

QUAT HPV CHALLENGE TASK GROUP

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Summary

The member companies of the Quat HPV Challenge Task Force hereby submit for review and public comment their test plan for the family of chemical substances known as "quats" under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Challenge Program.

The quaternary ammonium salts of the esters of acrylic and methacrylic acid, dimethylaminoethylacrylate and dimethylaminoethylacrylate represent a category for the purposes of the HPV Challenge Program. Briefly, the ester precursor is produced by reaction of dimethylaminoethanol with acrylic acid or methacrylic acid, producing either dimethylaminoethylacrylate (ADAM) or dimethylaminoethylmethacrylate (MADAM), respectively. These esters differ from each other by one carbon in the acrylic chain. The tertiary amine moiety is caustic and lacks stability. In order to alleviate these characteristics, the tertiary amine is reacted with either methyl chloride (MC) or dimethyl sulfate (DMS) to produce a more stable and less caustic quaternary amine salt. So, both ADAM and MADAM have both a methyl chloride salt (ADAMMC and MADAMMC) and a dimethyl sulfate salt (ADAMDMS and MADAMDMS). The toxicity and physical chemical properties of these quaternary ammonium salts are very similar, as would be expected. The tertiary amine salts have been used as the surrogate for the category as they have been tested extensively (SIDS Dossier ID 2439-35-2 [ADAM] and SIDS Dossier ID 2867-47-2 [MADAM]).

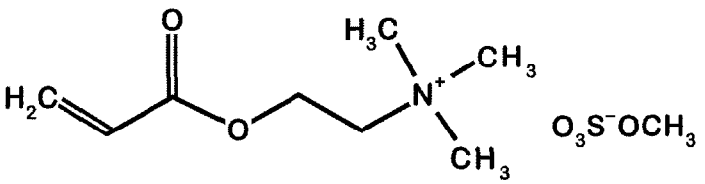
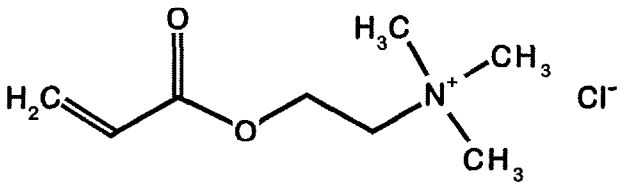
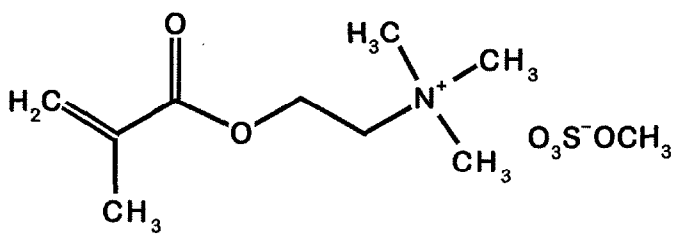
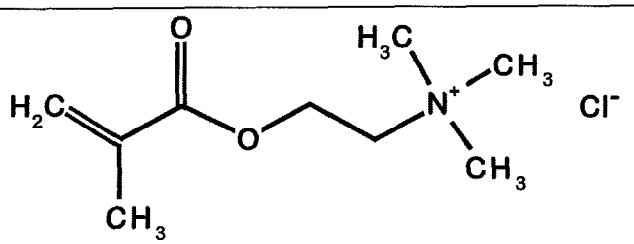
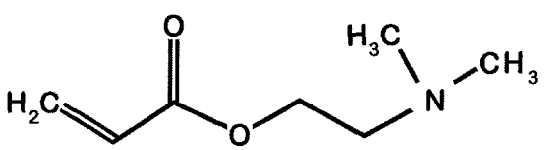
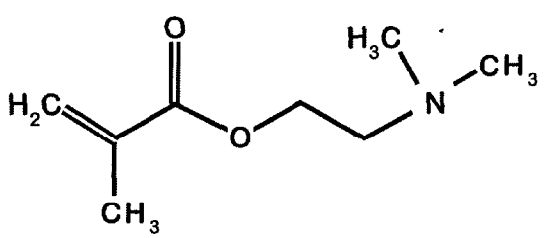
Note: Since the initiation of the HPV program, the production volume of ADAMDMS and both MADAM salts have dropped substantially. It is unlikely that the current magnitude of production still qualifies these substances as HPV chemicals.

Proposed Test Plan

No further testing is necessary on this category.

Identity, Chemistry and Basis of Category

The quaternary ammonium salts of the acrylic acid esters dimethylaminoethylacrylate and dimethylaminoethylmethacrylate represent a category for the purposes of the HPV Challenge Program. Briefly, the ester precursor is produced by reaction of dimethylaminoethanol with acrylic acid or methacrylic acid, producing either dimethylaminoethylacrylate (ADAM, CASRN 2439-25-2) or dimethylaminoethyl-methacrylate (MADAM, CASRN 2867-47-2). These esters differ from each other by a methyl group on the acrylic chain. The tertiary amine moiety is caustic and lacks stability. In order to alleviate these characteristics, the tertiary amine is reacted with either methyl chloride or dimethyl sulfate to produce a more stable and less caustic quaternary amine salt. So, both ADAM and MADAM have both a methyl chloride (MC) salt (ADAMMC and MADAMMC) and a dimethyl sulfate (DMS) salt (ADAMDMS and MADAMDMS). The toxicity and physical chemical properties of these quaternary ammonium salts are very similar, as would be expected. The tertiary amine salts have been used as surrogates for the category as they has been tested extensively with IUCLID and SIDS documents available on both: (SIDS Dossier ID 2439-35-2; SIDS Dossier ID 2867-47-2). The structures of the quaternary ammonium salts as well as their acid ester precursors are shown below.

Quaternary Ammonium Salts	
	Dimethylaminoethylacrylate, dimethyl sulfate (ADAMDMS, CASRN 13160-44-0)
	Dimethylaminoethylacrylate, methyl chloride (ADAMMC, CASRN 44992-01-0)
	Dimethylaminoethylmethacrylate, dimethyl sulfate (MADAMDMS, CASRN 6891-44-7)
	Dimethylaminoethylmethacrylate, methyl chloride (MADAMDMS, CASRN 5039-78-1)
Esters of Acrylic and Methacrylic Acids	
	Dimethylaminoethylacrylate (ADAM, CASRN 2439-35-2)
	Dimethylaminoethylmethacrylate (MADAM, CASRN 2867-47-2)

Summary of Exposure and Test Data

ADAM and MADAM are quaternized with either methyl chloride or dimethyl sulfate in a closed system to produce ADAMMC, ADAMDMS, MADAMMC and MADAMDMS. These quaternary ammonium salts are then polymerized to form homopolymers and copolymers with other monomers (mainly with acrylamide), in a closed system to produce cationic water-soluble polymers. Polymerization is the only use of these chemicals. The polymers are used for waste-water and sludge treatment, paper manufacture, mining and other uses. There is virtually no human exposure to the quaternized salts.

The quaternary salts have very low environmental toxicity. They have very low toxicity to fish and daphnia and have an algal LC50 greater than 1 mg/L. They have a low order of toxicity to laboratory animals. They are not irritating to the skin, moderately irritating to eyes and are dermal sensitizers

ADAM has been tested in subchronic gavage studies and induces gastric hyperplasia in the stomach. It is not teratogenic and docs it does not induce reproductive effects (SIDS Dossier ID 2439-35-2).

We conclude that there is sufficient data on the quats and their unquaternized acrylic acid esters that no further testing is needed on this category at this time.

Test Data

The test conducted on the quats as well as on the esters of acrylic and methacrylic acid are shown in the following table:

Environmental Studies	ADAM MC	ADAM DMS	ADAM	MADAM MC	MADAM DMS	MADAM
Acute fish toxicity	✘	✘	✘	✘	✘	✘
Acute daphnid toxicity	✘	✘	✘	✘	✘	✘
Acute algal inhibition	✘	✘	✘	✘	✘	✘
Chronic algal inhibition	✘	✘	✘	✘	✘	✘
Effect on bacteria	✘	✘	✘	✘	✘	✘
Biodegradability	✘	✘	✘	✘	✘	✘
Human Health Studies						
Acute oral toxicity	✘	✘	✘	✘	✘	✘
Ames test	✘	✘	✘	✘	✘	✘
Primary skin irritation	✘	✘	✘	✘	✘	✘
Acute eye irritation	✘	✘	✘	✘	✘	✘
Sensitization	✘	✘	✘	✘	✘	✘
Human lymphocytes	✘	✘	✘	✘	✘	✘
Mouse lymphoma	✘	✘	✘	✘	✘	✘*
Subchronic toxicity	✘	✘	✘	✘	✘	✘
Reproductive effects	✘	✘	✘	✘	✘	✘

* Chinese hamster cells were tested rather than mouse lymphoma

TOXICITY TO AQUATIC ORGANISMS

Tests Conducted on Aquatic Organisms: ADAMMC			
Study	**Species**	**Strain**	**Result**
Acute Toxicity (96h)	Fish	Zebra Fish	LC50 > 100 mg/l
Immobilization (48h)	Daphnia	*Dapnia magna*	EC50 > 100 mg/l
Growth inhibition (72h)	Algae	*Scenedesmus subspicatus*	1 < IC50 < 10 mg/l
Growth inhibition (72h)	Algae	*Scenedesmus subspicatus*	IC50 = 0.65 mg/l
Tests Conducted on Aquatic Organisms: ADAMDMS			
Acute Toxicity (96h)	Fish	Zebra Fish	LC50 > 100 mg/l
Immobilization (48h)	Daphnia	*Dapnia magna*	EC50 > 100 mg/l
Growth inhibition (72h)	Algae	*Scenedesmus subspicatus*	1 < IC50 < 10 mg/l
Tests Conducted on Aquatic Organisms: MADAMMC			
Acute Toxicity (96h)	Fish	Zebra Fish	LC50 > 100 mg/l
Immobilization (48h)	Daphnia	*Dapnia magna*	EC50 > 100 mg/l
Growth inhibition (72h)	Algae	*Scenedesmus subspicatus*	IC50 > 100 mg/l
Tests Conducted on Aquatic Organisms: MADAMDMS			
Acute Toxicity (96h)	Fish	Zebra Fish	LC50 > 100 mg/l
Immobilization (48h)	Daphnia	*Dapnia magna*	EC50 > 100 mg/l
Growth inhibition (72h)	Algae	*Scenedesmus subspicatus*	10 < IC50 < 100 mg/l
Tests Conducted on Aquatic Organisms: ADAM (*i.e.*, non-quaternized)*			
Acute Toxicity (96h)	Fish	Zebra Fish	LC50 > 8.5 mg/l
Immobilization (48h)	Daphnia	*Dapnia magna*	EC50 > 9.9 mg/l
Growth inhibition (72h)	Blue-green	*Scenedesmus subspicatus*	IC_A50 = 0.23 mg/l
Tests Conducted on Aquatic Organisms: MADAM (*i.e.*, non-quaternized)*			
Acute Toxicity (96h)	Fish	Goldfish	LC50 = 139.5 mg/l
Immobilization (48h)	Daphnia	*Dapnia magna*	EC50 = 53mg/l

*Data from OECD HPV SIDS dossier

Quaternized ammonium salts have a low order of aquatic toxicity. The table above summarizes the aquatic toxicity tests carried out. These monomers have no toxicity to multi-cellular organisms. For fish, the LC50s at 96 hours are all greater than 100 mg/L (Calmels, 1994a; Calmels, 1994b; Calmels, 1994c). Similarly, for daphnia, the EC50s (immobilization) at 48 hours are all greater than 100 mg/L (Calmels, 1994d; Calmels, 1994e; Calmels, 1994f). They demonstrate significant effects on the growth of the most sensitive algal test species *Scendesmus subspicatus*, especially the ADAM quats (Licata-Messana, 1994a; Licata-Messana, 1994b). This is common among quaternized ammonium salts. However, in this case, the effect is most likely the result of the hydrolysis of the residual ester of acrylic acid to acrylic acid (ADAM) and methacrylic acid (MADAM). Acrylic acid demonstrates a high degree of inhibition on the growth of this species (EC50/72 hours = 0.004 mg/l) while methacrylic acid demonstrates a lower effect (1 < IC50 < 10 mg/l). The aquatic toxicity of ADAM and MADAM from their respective OECD HPV SIDS dossiers has been included for completeness (SIDS Dossier ID 2439-35-2).

ENVIRONMENTAL FATE

Environmental Fate Studies		
Substance	**Study**	**Result**
ADAMMC	OECD TG 302B: Inherent Biodegradability, Zahn-Wellens Test	85% in 27 days
MADAMMC	OECD TG 301B: Ready Biodegradability. CO_2 Evolution (Modified Sturm Test)	69% in 28 days

ADAMMC has been tested for inherent biodegradability (Wehrhahn, 1999). It was found to be biodegradable to 85% in 27 days. MADAMMC has been tested for ready biodegradability (Thiébaud, 1996) and was found to be biodegradable to 69% in 28 days. From these test results it can be deduced that all the quats are highly biodegradable.

No further environmental testing is necessary for this category of chemicals.

ACUTE TOXICITY

Acute Toxicity Tests Conducted *In Vivo* on ADAMMC			
Study	**Species**	**Strain**	**Result**
Acute Oral Toxicity	Rat	Sprague-Dawley	LD50 = 1600 mg/kg
Primary Skin Irritation	Rabbit	New Zealand White	0.0 (Not irritating to skin)
Acute Eye Irritation	Rabbit	New Zealand White	25 on Day 1 (Moderate)
Sensitization	Guinea Pig	Dunkin-Hartley	Sensitizing
Acute Toxicity Tests Conducted *In Vivo* on MADAMMC			
Study	**Species**	**Strain**	**Result**
Acute Oral Toxicity	Rat	Sprague-Dawley	LD50 = 1300 mg/kg
Acute Toxicity Tests Conducted *In Vivo* on ADAM*			
Study	**Species**	**Strain**	**Result**
Acute Oral Toxicity	Rat	Sprague-Dawley	LD50 = 455 mg/kg
Acute Dermal Toxicity	Rat	Sprague-Dawley	LD50 = 419 mg/kg
Acute Inhalation Toxicity	Rat	Sprague-Dawley	LC50/4 hours = 0.066 mg/l
Primary Skin Irritation	Rabbit	New Zealand White	8.0 (Corrosive)
Acute Eye Irritation	Rabbit	New Zealand White	49 on Day 1 (Corrosive)
Sensitization	Guinea Pig	Hartley-Dunkin	Sensitizing
Acute Toxicity Tests Conducted *In Vivo* on MADAM*			
Study	**Species**	**Strain**	**Result**
Acute Oral Toxicity	Rat	Sprague-Dawley	LD50 = 1,550 mg/kg
Acute Dermal Toxicity	Rat	Sprague-Dawley	LD50 > 3,000 mg/kg
Acute Inhalation Toxicity	Rat	Sprague-Dawley	LC50/4 hours = 0.62 mg/l
Primary Skin Irritation	Rabbit	New Zealand White	5.97 (Corrosive)
Acute Eye Irritation	Rabbit	New Zealand White	Corrosive
Sensitization	Guinea Pig	Hartley-Dunkin	Sensitizing

*Data from OECD HPV SIDS dossier

Acute Toxicity

The acute oral toxicity of ADAMMC and MADAMMC are very similar. The results are summarized in the above table. The LD50s for both materials are around 1600 and 1300 mg/kg, respectively (Collier, 1985d; Clouzeau, 1990). ADAMMC is not irritating to the skin but produces moderate eye irritation (Collier, 1985b; Collier, 1985c). MADAMMC and ADAMMC are both dermal sensitizers (Collier, 1985a). In contrast, ADAM, which is a tertiary, not a quaternary amine, has an oral LD50 in the rat of 455 mg/kg due primarily to gastric toxicity (SIDS Dossier ID 2439-35-2). It causes eye and skin burns and is also a sensitizer.

No testing is necessary for the acute toxicity or irritancy of these materials.

Mutagenicity

Mutagenicity Tests on the Quaternized Acrylic Esters				
Test Substance	**Ames Salmonella Microsome**	**L5178 Mouse Lymphoma**	**Human Lymphocyte Cytogenetics**	**Mouse Micronucleus**
MADAMMC	Negative	Negative	Negative	Not Done
MADAMDMS	Negative	Negative	Negative	Not Done
ADAMMC	Negative	Negative	Negative	Not Done
Mutagenicity Tests on the Acrylic Esters**				
MADAM	Negative	Negative	Positive*	Negative
ADAM	Positive	Not Done	Positive	Negative

* Chinese hamster cells were tested

** Data from OECD HPV SIDS dossier (SIDS Dossier ID 2439-35-2; SIDS Dossier ID 2867-47-2).

ADAMMC, MADAMMC MADAMDMS have been tested *in vitro* for gene mutations (Adams, 1990b; Clouzeau, 1991a; Clouzeau, 1991b; Wollny, 1997) and chromosomal aberrations (Adams 1990a). They are negative in these mutagenicity studies. For

completeness, we have included the results from mutagenicity tests of ADAM and MADAM.

Repeated dose toxicity

Quaternized acrylate esters have not been tested in repeat dose toxicity studies. Rather, the tertiary amine acrylate ester, dimethylaminoethyl acrylate (ADAM) has been tested. Two oral administration studies have been located (SIDS Dossier ID 2439-35-2).

Study 1: Parental toxicity

One of the oral studies was conducted according to OECD Test Guideline 422 in compliance with GLP (SIDS Dossier ID 2439-35-2). This was a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test. Groups of 12 Sprague Dawley (Crl: CD) rats were administrated doses of 0 (vehicle; corn oil), 4, 20, and 100 mg of ADAM per kg bodyweight per day by gavage. The dosing period for males was 43 days, and females were dosed from 14 days before mating to day 3 of lactation. The results were summarized below.

Males

At 100 mg/kg/day, the following adverse effects were observed; a transient suppression of body weight gain, a decrease in food consumption, thickening of the wall of the forestomach, pancreatico-duodenal lymph nodes. Hyperplasia of plasma cells in the pancreatico-duodenal lymph nodes was observed. Increase ratio in reticulocyte, platelet and segmented neutrophil counts and decrease in albumin was observed. At 20 and 100 mg/kg/day, ulceration, inflammatory cell infiltration and hyperplasia of the mucosa were observed in the forestomach. However, histopathological changes in forestomach were considered toxicologically insignificant because these changes were based on stimulative of this chemical. At 4 mg/kg/day, no effects were observed. The NOAEL for males was considered as 20 mg/kg/day.

Females

In 100 mg/kg/day group, 2 females out of 12 died. Thickening of the wall of the forestomach, pancreatico-duodenal lymph nodes and atrophy of the thymus were observed. Ulceration, inflammatory cell infiltration and hyperplasia of the mucosa in the

forestomach and hyperplasia of plasma cells in the pancreatico-duodenal lymph nodes were observed. At 4 and 20 mg/kg/day, no effects were observed. Thus the NOAEL for females was considered as 20 mg/kg/day.

The NOAEL for the repeat dose toxicity is considered to be 20 mg/kg/day for both sexes.

Reproductive Phase

Reproductive parameters such as mating index, fertility index, number of corpora lutea or implantations, implantation index, gestation index, delivery index, gestation length, parturition or maternal behavior were not effected by compound administration. There were no compound related changes in number of offspring, sex ratio, live birth index, and viability index or body weight. Additionally, no abnormal findings were observed at external features, clinical signs or necropsy. Therefore, there are no effects by the compound on the reproductive performance of the parent animals and growth of the offspring. The NOAELs for reproductive/development toxicity test are considered to be 100 mg/kg/day, the highest dose tested, for parental animals and offspring.

Study 2

The second study was conducted according to the OECD Test Guideline for repeated dose 90-day oral toxicity study in rodents [OECD TG 408] (SIDS Dossier ID 2439-35-2). Groups of Sprague Dawley (Crl: CD) rats were treated with doses of 0 (vehicle; peanut oil), 2, 10, and 50 mg/kg/day by gavage. The dosing period for males and females was 13 weeks. The results were summarized below.

Twenty rats/sex for control group, 10 rats/sex for low and intermediate dose-levels and 25 rats/sex for high dose-level were used. Thirteen males and 9 females died or were sacrificed moribund at 50 mg/kg/day. Twenty-one of these deaths (except one male) occurred during the exposure period. The cause of death was lung lesions, which were considered to be due to direct irritation from regurgitated stomach contents. No compound related clinical signs were observed at 2 and 10 mg/kg/day. Ptyalism and/or loud breathing were observed in a few animals at 50 mg/kg/day. Slight reduction in body weight gain was observed at 50 mg/kg/day in males and in all treatment groups in females. However, it was transient and not significant. There were no effects at 2 and 10 mg/kg/day. But, there was a slight increase in neutrophil counts and decrease in

lymphocyte counts. There were no changes in absolute and relative organ weight. There were no effects at food consumption, ophthalmology, blood biochemistry and urinalysis. In macroscopic examination, there were no effects at 2 and 10 mg/kg/day. At 50 mg/kg/day, grayish foci in the mucosa of the forestomach in 11/20 males and 13/19 females, enlargement of the pancreatic lymph nodes in 5/20 males and 6/19 females, dilatation or reddish color of the lungs in 7/20 males and 6/19 females were observed. In microscopic examination, hyperplasia/hyperkeratosis and edema and inflammatory cell infiltration of the forestomach submucosa were observed at 10 mg/kg/day. At 50 mg/kg/day, ulceration, hyperplasia/hyperkeratosis, infiltration or granulation tissue formation in the submucosa, oedema in mucosa and submucosa and necrosis of the mucosa/submucosa in forestomach, alveolar haemorrhage or edema and congestion in lungs were observed. These findings were considered to be a direct irritant effect or an effect of regurgitation of stomach contents.

The NOAEL for the repeat dose toxicity is considered to be 10 mg/kg/d

Reproductive phase

According to the OECD test guidelines 414, SD (Crl: CD) rats were administrated doses of 0 (vehicle; peanut oil), 10, 30 and 100 mg/kg/day by gavage. Females were dosed from day 6 to day 15 after mating was confirmed. The results are summarized below.

Twenty-five females for each group were used. Two females died at 30 mg/kg/day, one was killed prematurely at 100 mg/kg/day. Some clinical signs (principally loud breathing, piloerection, chromorhinorrhea, round back and dyspnea) were observed in a few female at the 30 and 100 mg/kg/day. No abortions occurred in any female. No total resorptions occurred in any female except one at 100 mg/kg/day. Reduction in food consumption and body weight gain were observed slightly at 100 mg/kg/day. In macroscopic examination, there were no effects at 10 mg/kg/day. At 30 and 100 mg/kg/day, gastrointestinal tract (gaseous dilatation or thickening of mucosa) were observed in 3/25 and 6/25 females, respectively. These findings were principally observed in the decedent animals. At 100 mg/kg/day, the post-implantation loss was slightly increased and the body weight of the fetuses was decreased. The number of live fetuses and sex-ratio were not affected.

In fetal observations: The following were found at 100 mg/kg/day. Twenty-seven/299 fetuses were malformed (14 fetuses from the same litter were dwarf, 13 other fetuses

from another litter suffered aphalangy). Two/144 fetuses were malformed (one fetus had a cleft palate, another fetuses presented hydrocephaly). Additionally, six dwarf fetuses suffered testicular ectopia. Reduced ossification or absence of ossification of many bones (head, vertebrae, sternebrae, limbs and paws) were also found at 30 mg/kg/day. The incidence for the absence of ossification of 6th sternebra was increase at 100 mg/kg/day. The NOAELs for development toxicity/teratogenicity test are considered to be 10 mg/kg/day for embryotoxicity and fetotoxicity, and to be 30 mg/kg/day for teratogenicity.

BACKGROUND INFORMATION

Method of manufacture

Quaternized ammonium salts (quats) are manufactured by derivitizing the corresponding tertiary amine. Methylchloride and dimethylsulfate are the derivitizing agents used. Production of the quaternary amine results in a more stable and cationic monomer.

Commercial Application

Quats are essentially copolymerized with acrylamide and sometimes with other monomers or homopolymerized to produce cationic, water-soluble polymers. These polymers are used for waste-water and sludge treatment, sugar processing, paper manufacture, mining and several other applications. The polymer contains trace levels of monomers.

Shipping

In United States, quats are generally polymerized at their manufacturing site. A percentage of quats enters interstate commerce, but generally only the polymer moves in commerce. When transported, it is sold in bulk as tank wagons or rail cars.

Worker Exposure

Quats are manufactured and polymerized in closed systems. They are easily pumped as they are liquid. No significant worker exposure occurs.

Consumer Exposure

There are no consumer applications for these chemicals.

Conclusion

This category of quaternized amino acrylate esters is used as starting monomers in closed systems. They are manufactured in zero discharge facilities with no significant human or environmental exposure. The tertiary amine, dimethylaminoethylacrylate, has been extensively tested. This substance has no reproductive or developmental toxicity and has

a NOAEL in rats of 10 mg/kg/day. Members of this category are more chemically stable, do not share the same propensity to cause gastric toxicity and therefore are expected to be substantially less toxic. In the absence of exposure and with substantial data on a structural congener, no further testing is recommended.

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